

Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV positive patients on Anti Retroviral therapy (ART)

Dissertation submitted in partial fulfilment of the
University regulations for the award of the degree of

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(M.D General Medicine)

Branch I

Of

THE TAMILNADU Dr.M.G.R. MEDICAL
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CHENNAI, INDIA.



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DECLARATION

I solemnly hereby declare that this dissertation entitled **“Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV positive patients on Anti Retroviral therapy (ART)”** has been undertaken by me at the Madras Medical College, Chennai during 2008 - 2011 under the guidance of Dr.E.Dhandapani, professor of medicine, Dr. Ragunathanan, Professor of Medicine and under the supervision of Dr.Rajendiran, Professor and HOD, Department of Medicine, Madras Medical College, Chennai in partial fulfilment of the university regulations for the award of the degree of Doctor of Medicine (M.D. Medicine). This has not been submitted previously by me to any other University.

Place : Chennai

Date :

Signature of the Candidate

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CERTIFICATE

This is to certify that Dr. Sivaprakash .v has undergone the prescribed course of studies leading to the M.D Degree examination in Medicine in accordance with the rules and regulations of the Dr.M.G.R. University and the dissertation entitled **“Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV positive patients on Anti Retroviral therapy (ART)”** is a bonafide work.

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INTRODUCTION

Antiretroviral therapy (ART) has led to a significant decline in AIDS - associated morbidity and mortality (1). These benefits are in part a result of partial recovery of the immune system, manifested by increase in CD4 T-lymphocytes counts and decrease in plasma HIV-1 viral loads

(2). In some patients clinical deterioration occurs despite increased CD4 T-lymphocytes and decreased plasma HIV-1 viral loads

(3). This clinical deterioration is due to inflammatory response of the immune system to both subclinical pathogens and residual antigens.

In the mid-1990s, clinicians noticed that certain patients deteriorated after starting HAART despite having decreasing HIV-1 RNA levels and rising CD4 cell counts [\[2-5\]](#). In these patients, receipt of HAART results in a pathological inflammatory response to either previously treated infections or subclinical infections [\[6-8\]](#). This inflammation could result in deleterious clinical outcomes, such as culture-negative meningitis or necrotizing lymphadenitis; it has been labeled as immune reconstitution disease (IRD) or immune reconstitution inflammatory syndrome (IRIS) [\[9-11\]](#).

Immune Reconstitution Inflammatory Syndrome (IRIS) is defined as a paradoxical deterioration in clinical status after initiating anti -retroviral therapy

attributable to the recovery of the immune response to latent or subclinical infection or non-infectious processes.

Despite numerous descriptions of the manifestations its pathogenesis remains speculative. Current theories concerning the pathogenesis of IRIS involves a combination of underlying antigenic burden, a degree of immune restoration following anti-retroviral therapy and host genetic susceptibility.

Immune Reconstitution Inflammatory Syndrome (IRIS) that occurs as a result of “unmasking” of clinically silent infection is characterized by atypical exuberant inflammation or an accelerated clinical presentation suggesting a restoration of antigen-specific immunity.

Following anti- retroviral therapy an increase in memory CD4 cell types is observed (4) possibly as a result of redistribution from peripheral lymphoid tissue (5). This CD4 is primed to recognize previous antigenic stimuli and be responsible for the manifestations of Immune Reconstitution Inflammatory Syndrome (IRIS) seen soon after initiation of Anti Retroviral therapy.

The best described associations between particular infectious agents and IRIS include ophthalmic cytomegalovirus (CMV) disease, disseminated infection with *Mycobacterium tuberculosis* or *Mycobacterium avium* complex, and central nervous system involvement with *Cryptococcus neoformans* .

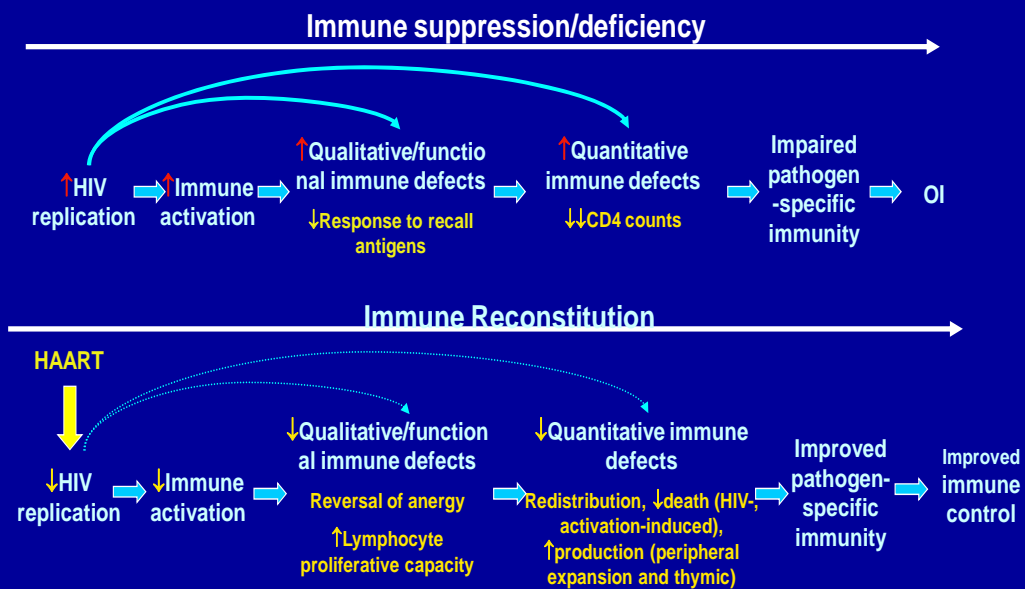
Risk Factors :

- Advanced HIV disease - CD4 counts <50
- Unrecognized Opportunistic infection or high microbial burden
- Early initiation of HAART
- ARV naïve
- Immune recovery with rapid fall in HIV RNA
- Genetic factors which can be pathogen specific

Mycobacteria – TNF-308*2, IL6 – 174*G

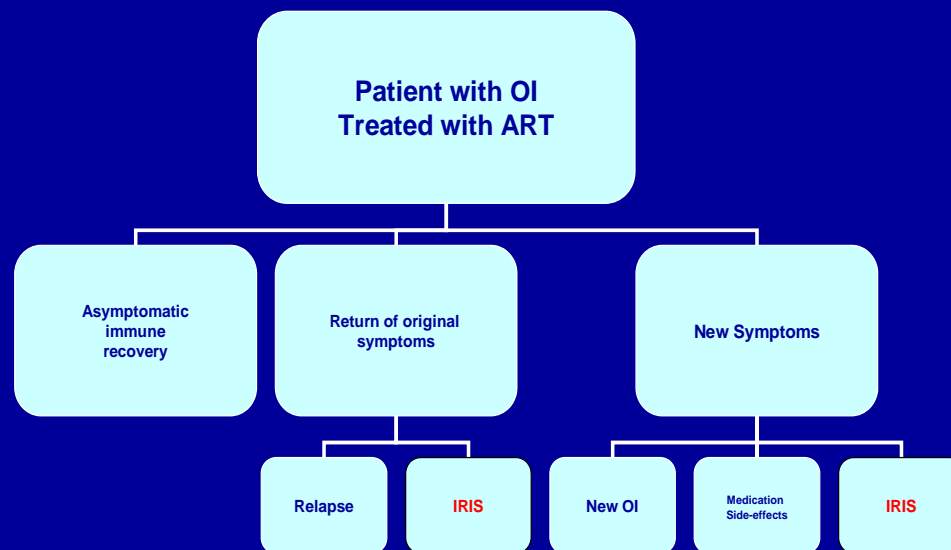
Herpes virus - HLA- B44, -A2, -DR2, IL12B3'UTR*1

Antiretroviral Therapy Improves Qualitative and Quantitative Immune Defects

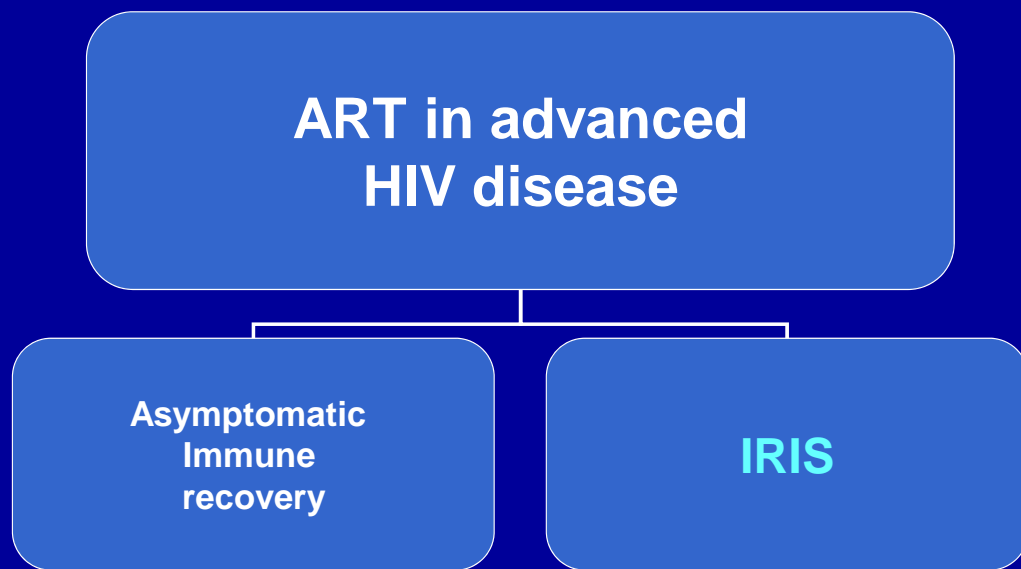


Migueles, Buenos Aires 2003

ART and the treatment of OIs



ART with subclinical infection



TB- IRIS :

- Well recognized phenomenon for decades
- Lymphadenitis (12 – 25 %),
- 1 – 6 months post initiation of therapy
- Pulmonary disease, central nervous system-new tuberculomas, fevers, ARDS
- 75% have worsening of original lesions
- Often required steroids
- Due to intensification of the cell mediated immune response and conversion of TST
- Concomitant rise in TNF levels

We have very few studies about Immune Reconstitution Inflammatory Syndrome and most of it is Western Studies.

The incidence, risk factors and presentation of IRIS may differ in our Indian context.

As we have very few Indian studies about IRIS, a study is planned to find the clinical spectrum of IRIS in HIV positive patients visiting a tertiary care centre at the chennai.

The present study was undertaken to determine the incidence of IRIS in high-risk patients, the risk factors at baseline for developing IRIS, and the long-term outcome of patients with IRIS.

We hypothesized that patients who started HAART in closer proximity to the diagnosis of their underlying opportunistic infection and who had a more robust response to HAART in terms of increasing CD4 levels would be at an increased risk for developing IRIS.

Aim :

To study the profile of Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV positive patients on Anti Retroviral therapy (ART)

Objectives :

1. Type of Opportunistic Infections
2. Correlation with the CD 4 count

REVIEW OF LITERATURE

Immune Reconstitution Inflammatory Syndrome (IRIS)

- IRIS can be described as an adverse clinical phenomenon following rapid restoration of immune function in a previously severely immune-compromised individual.
- This is not specific to HIV positive persons on ART but can follow recovery from neutropenia (chemotherapy/transplantation) or dose reduction/withdrawal of steroids.
- The syndrome is well-described for many bacteria, virus, fungi, protozoa, helminth, virus related malignancy and non-infectious processes.
- In HIV-infected patients, IRIS can be described as a deterioration of the opportunistic infection due to restoration of pathogen specific immune responses.

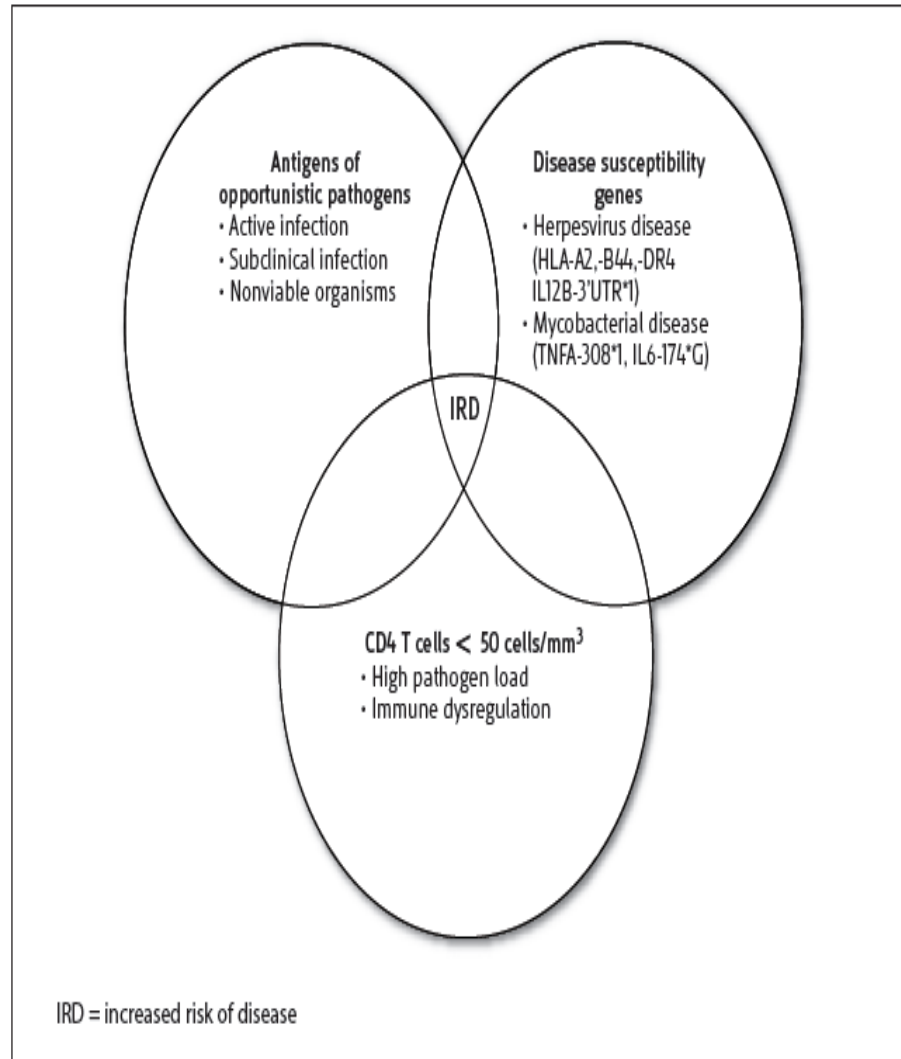


FIG 1. PATHOGENESIS AND RISK FACTORS OF IRIS

Etiology	Class of pathogen	Specific pathogen or disease
Infectious	Mycobacteria and bacteria	<i>Mycobacterium tuberculosis</i> ^{10,12} <i>Mycobacterium avium</i> complex ^{10,23} <i>Mycobacterium leprae</i> ^{14,15} <i>Bartonella henselae</i> ⁵ <i>Chlamydia trachomatis</i> (as Reiter's syndrome) ¹⁶
	Fungi	<i>Cryptococcus neoformans</i> ^{17,20} <i>Pneumocystis jirovecii</i> ⁸ Histoplasma ²¹ Tinea (dermatophytes) ²²
	Viruses	Cytomegalovirus ^{23,24} Herpes simplex virus type 1 and 2 ²⁵ Hepatitis B and C ^{22,26,27} Varicella zoster virus ^{28,29} Human papillomavirus ³⁰ JC virus (as progressive multifocal leukoencephalopathy) ³¹ Parvovirus B19 (as encephalitis) ³²
	Protozoa	<i>Leishmania</i> spp. ^{33,34} Toxoplasma ²²
	Helminths	Schistosoma ³⁵ Strongyloides ³⁶
Virally driven malignancy		Eppstein-Barr virus (as non-Hodgkin's lymphoma) ³⁷ Human herpesvirus 8 (as Kaposi's sarcoma) ³⁸⁻⁴⁰
Presumed noninfectious		Systemic lupus erythematosus ⁴¹ Sarcoidosis ⁴² Grave's disease ⁴³
Possibly infectious		Guillain-Barré syndrome ⁴⁴ Appendicitis ⁴⁵ Eosinophilic folliculitis ^{46,47} Papular pruritic eruption ⁴⁷

FIG 2. INFECTIOUS AND NON-INFECTIOUS ETIOLOGY OF IRIS

DIAGNOSIS OF IRIS :

In India, the agreed practical definition of IRIS would be the **“occurrence or manifestations of new opportunistic infections or existing opportunistic infections within six weeks to six months after initiating anti-retroviral therapy with an increase in CD4 count”**

- Typically, IRIS occurs within 2–12 weeks of the initiation of ART, although it may present later (usually between 6 weeks to 6 months)
- The incidence of IRIS is estimated to be 10% among all patients in whom ART has been initiated; and up to 25% among those who have started ART and who have a CD4 cell count of below 50 cells/mm³

<p>Definition described by French et al⁶</p> <p>Must meet both major A and major B criteria, or major A and any two minor criteria.</p> <p>Major Criteria A</p> <p>Atypical presentation of opportunistic infections or tumors in patients responding to ART</p> <ul style="list-style-type: none"> ■ Localized disease (e.g., lymph nodes, liver, spleen) ■ Exaggerated inflammatory reaction (e.g., severe fever, painful lesions) ■ Atypical inflammatory response in affected tissues (e.g., granulomas, suppuration, necrosis, perivascular lymphocytic inflammatory cell infiltrate) ■ Progression of organ dysfunction or enlargement of preexisting lesions after definite clinical improvement with pathogen-specific therapy before ART and exclusion of treatment toxicity and new diagnoses <p>Major Criteria B</p> <ul style="list-style-type: none"> ■ Decrease in VL greater than 1 log <p>Minor Criteria</p> <ul style="list-style-type: none"> ■ Increased CD4 T-cell count after ART ■ Increase in an immune response specific to the relevant pathogen (e.g., delayed-type hypersensitivity response to mycobacterial antigens) ■ Spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuation of ART
<p>Definition cited by Robertson et al⁷¹</p> <p>Must have all of the following:</p> <ul style="list-style-type: none"> ■ New onset or worsening symptoms of an infection or inflammatory condition following the initiation of ART ■ Symptoms not explained by a newly acquired infection, the predicted course of a previously diagnosed infection, or the adverse effects of drug therapy ■ Demonstration of a decrease of greater than or equal to 1 log in the number of HIV RNA copies

FIG 3. CASE DEFINITIONS OF IRIS

UNUSUAL PRESENTATIONS OF IRIS :

- Unexpected localized disease, e.g. lymph nodes (appearance or enlargement and/or suppuration), or involving liver or spleen
- Exaggerated inflammatory reaction, e.g. severe fever, with exclusion of other causes
- Painful lesions
- Atypical inflammatory response in affected tissues, e.g. granulomas, suppuration, necrosis
- Perivascular lymphocytic inflammatory cell infiltrate
- Progression of organ dysfunction or enlargement of pre-existing lesions
- Development or enlargement of cerebral space-occupying lesions after treatment for cerebral cryptococcosis or toxoplasmosis
- Progressive pneumonitis or the development of organizing pneumonia after treatment for pulmonary MTB or PCP

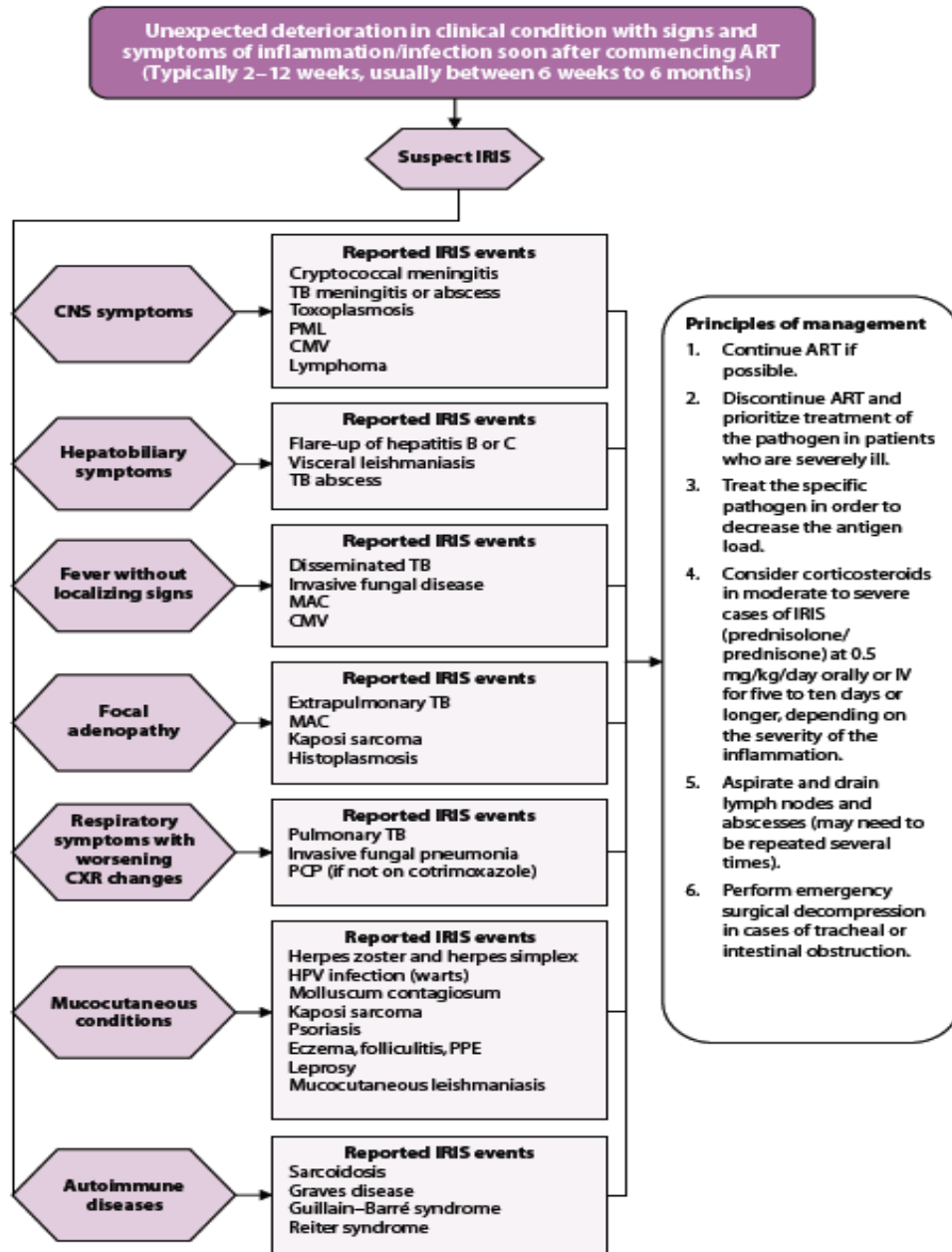


FIG 4. DIAGNOSTIC PROTOCOL FOR IRIS

Outcome	Number of studies	Incidence of outcome	Time on antiretroviral therapy (ART) before event	Risk factors (number of studies)
Any IRIS (unselected cohort) ^{55,56}	2	10.4%–22.7%	Median 7–12 weeks	Lower baseline CD4:CD8 ratio (1) Lower baseline CD4% (1) Lower baseline CD4 count (1)
Major opportunistic infection (OI) early in ART ^{22,30,57,58}	4	5.9%–25%	Within 20 weeks in 50% and 8 weeks in 68% of cases	Lower baseline CD4 count (3) Higher baseline viral load (1) Higher final CD4 count (1) CDC stage C (1) Younger age (1)
TB IRIS in patients with known TB (high-resource settings) ^{9,49,51}	4	30%–43%	Median 2–7 weeks	Greater decrease in viral load (2) Shorter time between OI diagnosis and ART initiation (2) Greater increase in CD4:CD8 ratio (1) Greater increase in CD4% (1) ART naive (1)
TB IRIS in patients with known TB (resource-limited settings) ^{48,52,53}	3	7.6%–12.6%	Median 2–6 weeks	Extrapulmonary TB (1) Shorter time between OI diagnosis and ART (1) Lower baseline CD4 (1)
Cryptococcal IRIS in patients previously treated for cryptococcal infection ^{30,49,54}	3	8.3%–33.9%	Median 4–34 weeks	Shorter time between OI diagnosis and ART initiation (2) Higher level of cerebrospinal fluid cryptococcal antigen (1) Fungemia (1) HIV infection revealed by cryptococcosis (1) ART naive (1) Higher baseline viral load (1)
<i>Mycobacterium avium</i> complex (MAC) IRIS in patients with known MAC ⁴⁸	1	31.4%	Not specified	Greater decrease in viral load (1) Shorter time between OI diagnosis and ART initiation (1) ART naive (1)

FIG 5. SUMMARY OF INCIDENCE AND RISK FACTORS OF IRIS IN PUBLISHED COHORTS

- IRIS—paradoxical reaction (deterioration of known condition that would otherwise be expected to improve)
- IRIS—unmasking (new clinical presentation of undiagnosed but preexisting condition)
- Failure of OI treatment because of drug-resistant organism
- Failure of OI treatment because of nonadherence to OI treatment or prophylaxis
- Failure of ART because of drug resistance
- Failure of ART because of nonadherence to ART
- Failure of OI treatment or ART for other reasons (e.g., malabsorption)
- Newly acquired OI or other condition
- Expected course of preexisting OI or other condition
- Adverse drug reaction

FIG 6. DIFFERENTIAL DIAGNOSIS OF IRIS

Condition	Clinical approach	Treatment
Paradoxical IRIS (worsening of known infection or condition)	<ul style="list-style-type: none"> ■ Patient education ■ Recognition of possible IRIS diagnosis ■ Consider secondary diagnoses 	<ul style="list-style-type: none"> ■ Continue ART; may stop if IRIS is life threatening ■ Optimize pathogen treatment and complete course ■ Consider steroids
Unmasking IRIS (emergence of undiagnosed infection or condition)	<ul style="list-style-type: none"> ■ Symptom-directed screening ■ Patient education ■ Expect atypical presentation 	<ul style="list-style-type: none"> ■ Continue ART; may stop if IRIS is life threatening ■ Treat new pathogen ■ Consider steroids

FIG 7. GENERAL APPROACH TO IRIS

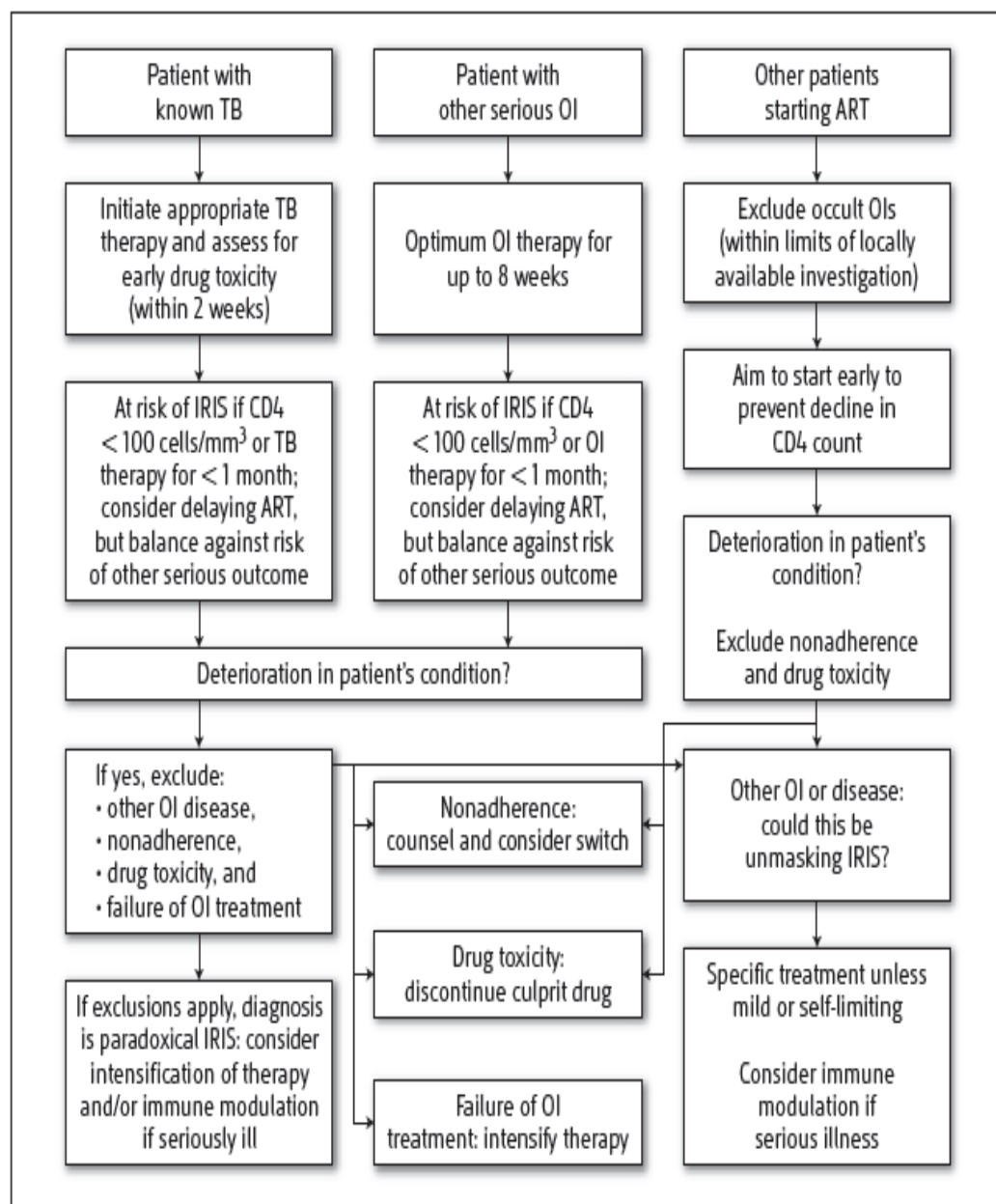


FIG 8. MANAGEMENT OF IRIS

Treatment of IRIS :

- There are no standard guidelines for the treatment of IRIS
- Milder forms of IRIS resolve with continuing anti-infective therapy and anti-retroviral therapy
- In the majority of cases, ART can be safely continued and need not be interrupted
- In general, most clinicians prefer to continue ART if the CD4 count is below 100/mm³ or if the patient presents with IRIS months after the initiation of ART
- However, the discontinuation of ART should be considered if the inflammatory responses are considered life-threatening (e.g. intracranial IRIS leading to encephalitis, cerebritis, perilesional cerebral oedema and pulmonary IRIS with ARDS/acute respiratory distress syndrome), or are unresponsive to steroids
- Discontinuation of the treatment should also be considered if the pathogens involved are not amenable to specific antimicrobials (e.g. Parvovirus B19, polyomavirus JC causing progressive multifocal leukoencephalopathy), Other Situations when HAART will likely need to be discontinued :

- Hepatitis →uncertainty about contribution of drug toxicity
- Skin eruptions – usually possible to differentiate cutaneous IRIS from drug rash.
- Non-steroidal anti-inflammatory drugs (NSAIDs) are helpful in controlling inflammation and fever associated with IRIS
- However, in severe IRIS, a short course of oral prednisolone is required to alleviate the symptoms
- The dosage and duration of treatment required is variable and should be judged clinically. Severe disease requires at least 1–2 mg of prednisolone per kg body weight
- In a study conducted by **Shelburne** et al ,To determine whether patients with IRIS require more interventions to prevent morbidity and mortality, they collected data regarding invasive procedures and hospitalizations during the first year following initiation of HAART as surrogate markers for healthcare utilization.
- In the 12 months after starting HAART, patients with IRIS required increased numbers of invasive procedures, such as lumbar punctures to relieve increased intracranial pressure, and had a higher number of hospitalizations. This implies that, in the short term, these patients require

intensification of their healthcare, thereby suggesting that preventive strategies might be cost effective. Such strategies might be especially effective in developing countries where coinfection with *C. neoformans* or *M. tuberculosis* is relatively common and the ability to manage complex paradoxical reactions readily may be limited [51].

Course of IRIS :

- Although there may be short-term morbidity associated with IRIS, these patients appear to have comparably good long-term outcomes. After 24 months of HAART, patients with IRIS were more likely to have successful viral suppression and immune reconstitution than patients without the syndrome. In addition, there was no significant mortality difference between the two groups of patients. In fact, the survival trend was in favor of the IRIS patients, which is likely a reflection of the durable viral suppression and immune reconstitution seen in these patients.

Previous Studies :

In a study by I. Ratnam, C. Chiu, N.-B. Kandala, and P. J. Easterbrook from Department of HIV/Genitourinary Medicine, King's College London, Guy's, King's College and St. Thomas' Hospitals, London, United Kingdom did a retrospective study of all patients starting HAART between 1 January 2000 and 31 August 2002 at a human immunodeficiency virus (HIV) clinic in London where a total of 199 patients were included, of whom 50.8% were male, 59.3% were black African, 29.1% were white, and 10.5% were black Caribbean. The median baseline CD4 cell count and HIV RNA load were 174 cells/L and 37,830 copies/mL respectively. Forty-four patients (22.7%) experienced an IRIS event at a median of 12 weeks after HAART initiation ; 22 events (50%) involved **genital herpes**, 10 (23%) involved **genital warts**, 4 (9.0%) involved **molluscum contagiosum**, and 4 (9.0%) involved **varicella zoster** virus infection. Five patients had **mycobacterial** infections, 4 had **hepatitis B**, 1 had *Pneumocystis jirovecii* infection, and 1 had **Kaposi sarcoma**. The strongest independent predictors of IRIS were **younger age** at initiation of HAART ($P=0.003$), **baseline CD4 cell percentage** (odds ratio [OR], 2.97) and **ratio of CD4 cell percentage to CD8 cell**.

Murdoch and David M did a prospective surveillance cohort and nested case-control study in a large university hospital-based antiretroviral therapy (ART) clinic where a total of 423 ART-naïve HIV-infected South African

patients were followed for signs and symptoms IRIS during the first 6 months of ART which was published in Journal of International of AIDS Society. During the first 6 months of ART, 44 (10.4%) patients experienced IRIS for an overall incidence rate of 25.1 cases per 100 patient-years. Diagnoses included **tuberculosis** (18/44, 41%), **abscess formation** and **suppurative folliculitis** (8/44, 18.2%), **varicella zoster** (6/44, 13.6%), **herpes simplex** (4/44, 9.1%), **cryptococcal meningitis** (3/44, 6.8%), **molluscum contagiosum** (3/44, 6.8%), and **Kaposi's sarcoma** (2/44, 4.5%). Median IRIS onset was **48 days** (interquartile range, 29-99) from ART initiation. In comparison with controls, IRIS cases had significantly **lower CD4 cell counts** at baseline (79 versus 142 cells/ μ l; $P= 0.02$) and at IRIS diagnosis (183 versus 263 cells/ μ l; $P = 0.05$), but similar virological and immunological response to ART. In multivariable analyses, higher baseline CD4 cell count was protective of developing IRIS (HR 0.72 per 50 cells/ μ l increase). Most IRIS cases were mild, with ART discontinued in three (6.8%) patients, corticosteroids administered to four (9.1%) patients, and hospitalization required in 12 (27.3%) patients. Two deaths were attributable to IRIS.

Weerawat Manosuthi , Sasisopin Kiertiburanakul, Thanongsri Phoorisri, Somnuek Sungkanuparph did a retrospective study in Bamrasnaradura Infectious Diseases Institute and Ramathibodi Hospital, Thailand were 167 patients with a mean age of 34.5 years, median CD4cell counts was 36 cells/mm³ and median HIV RNA was 427,000 copies/ml. ART was initiated at a median duration of 2.2

months after TB treatment. IRIS was identified in 21 (12.6%) patients. Patients with IRIS had a higher proportion of **extrapulmonary TB** than patients without IRIS ($P < 0.001$). By multivariate analysis, extrapulmonary TB was a risk factor for IRIS (odds ratio ≈ 8.225 , 95% confidence interval ≈ 1.785 – 37.911 , $P \approx 0.007$). Of 21 patients with IRIS, 15 patients developed IRIS within the first two months of ART. The mortality rate in patients with and without IRIS was not different.

Shelburne and Samuel did a retrospective cohort identified through a city-wide prospective surveillance program where a retrospective chart review was performed for 180 HIV-infected patients who received HAART and were coinfecting with *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, or *Cryptococcus neoformans* between 1997 and 2000. Medical records were reviewed for baseline demographics, receipt and type of HAART, response to antiretroviral therapy, development of IRIS, and long-term outcome. In this cohort, 31.7% of patients who received HAART developed IRIS. Patients with IRIS were more likely to have **initiated HAART nearer to the time of diagnosis of their opportunistic infection** ($P < 0.001$), to have been antiretroviral naive at time of diagnosis of their opportunistic infection ($P < 0.001$), and to have a **more rapid initial fall in HIV-1 RNA level** in response to HAART ($P < 0.001$).

Lawn and Stephen did a retrospective analysis of a study cohort enrolled over 3 years within a community-based ART service in South Africa. Patients receiving treatment for TB at the time ART was initiated (n = 160) were studied. Cases of TB-associated IRD during the first 4 months of ART were ascertained. The median baseline CD4 cell count was 68 cells/ μ l and ART was initiated after a median of 105 days from TB diagnosis. Although IRIS was diagnosed in just 12% (n = 19) of patients overall, IRIS developed in 32% (n = 12) of those who started ART within 2 months of TB diagnosis. **Pulmonary involvement** was observed in 84% (n = 16) and **intra-abdominal manifestations** were also common (37%). Overall, 4% (n = 7) of the cohort required secondary level health-care for IRIS and two (1%) patients died. In multivariate analysis, risk of IRIS was strongly associated with **early ART initiation** and **low baseline CD4 cell count**. Of patients with CD4 counts < 50 cells/ μ l, the proportions who developed IRD following initiation of ART within 0-30, 31-60, 61-90, 91-120 and > 120 days of TB diagnosis were 100%, 33%, 14%, 7% and 0%, respectively.

Manabe, Yukari C, Campbell, James D, Sydnor, Emily, Moor and Richard D did a study which was published in Journal of Acquired Immune Deficiency Syndromes Dec 2001. Here patients from the Johns Hopkins HIV Clinic who had IRIS were identified and matched with 4 controls without IRIS who had initiated HAART within 6 months of the case. Forty-nine cases of IRIS were identified. Patients presented a median of **29 days** from the initiation of

HAART (range: 4 to 186 days). A multivariate analysis showed that the development of IRIS was independently associated with using a **boosted protease inhibitor** (BPI) (odds ratio [OR] = 7.41; $P = 0.006$), a nadir **CD4 count** $<100 \text{ cells/mm}^3$ (OR = 6.2; $P < 0.001$), and a **plasma HIV viral RNA decrease of more than 2.5 log** at the time of IRIS compared with RNA levels before the initiation of HAART. Incrementally greater decreases in viral loads directly correlated with increased risk for the development of IRIS.

TB – IRIS :

- **Paradoxical reactions have been seen in TB prior to HIV thus IRIS phenomena in coinfectd pts may have been under reported**
- **29 - 36 % coinfectd pts on TB Rx and HAART develop clinically apparent IRIS**
- **Radiologic deterioration in 46%**
- **More frequent in HIV+ than HIV – patients**
- **36% (12/33) Narita M, et al. AJRCCM 1998;158:157.**
- **32% (6/19) Navas E, et al. ICAAC, 1999.**
- **6% (6/82) Wendel K, et al Chest 2001;120:193.**
- **30.2% (26/86) Shelburne S, et al AIDS 2005; 19:399**
- **Associated with restoration of TST reactivity**

- **Majority of cases of IRIS occurred in pts who were being treated for TB when HAART initiated**
- **Duration of TB Rx median = 2 months prior to IRIS presentation**
- **Duration of HAART median = 1month prior to IRIS presentation**
- **50% with undetectable HIV RNA at time of IRIS**
- **Median CD4# 205 from nadir of 51 (26 – 103)**

MATERIALS AND METHODOLOGY

This study is a **case control study** done on **HIV positive** patients on **Antiretroviral Therapy** at Government General Hospital at Chennai.

Immune Reconstitution Inflammatory Syndrome (IRIS) cases were diagnosed according to the latest **NACO guidelines**.

The **cases** included HIV positive patients who developed Immune Reconstitution Inflammatory Syndrome (IRIS) during Antiretroviral therapy (ART) and the **controls** included patients who did not develop IRIS during the ART.

Inclusion Criteria :

- 1). HIV positive patients on Anti Retroviral therapy of age > 18yrs with an increase in CD4 count
- 2). Occurrence of opportunistic infection (New OI) or worsening of symptoms (Existing OI) within 6 weeks to 6 months after initiation of Antiretroviral therapy

Exclusion Criteria :

- 1). Patient not on Anti Retroviral Therapy
- 2). Poor adherence
- 3). Defaulters

RESULTS AND ANALYSIS

This was a case control study where 50 IRIS cases were diagnosed in HIV positive patients on Antiretroviral therapy based on the NACO guidelines both retrospectively and prospectively which occurred between May 2008 to May 2010 and compared with 80 controls who were HIV positive patients on Antiretroviral therapy but did not develop IRIS.

The cases and controls were compared based on Age, Sex, Initial CD4 count, Final CD4 count, CD4 rise, Duration of ART, Type of ART and then the opportunistic infections and their relation to CD4 count was analysed.

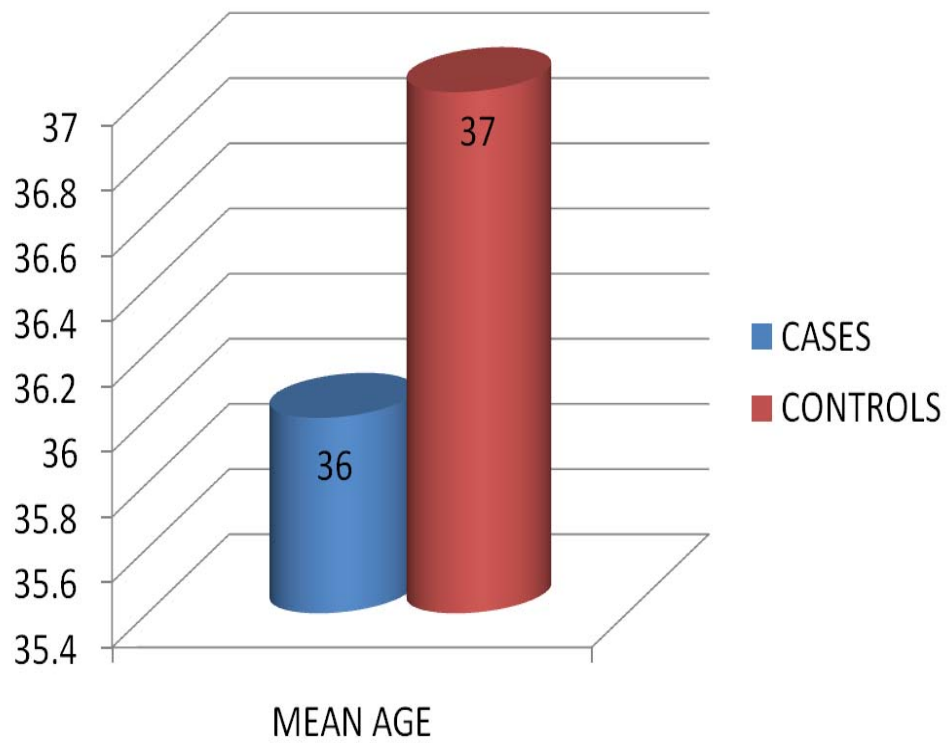


CHART 1 : AGE DISTRIBUTION

- The mean age of the cases is 36
- The mean age of the controls is 37

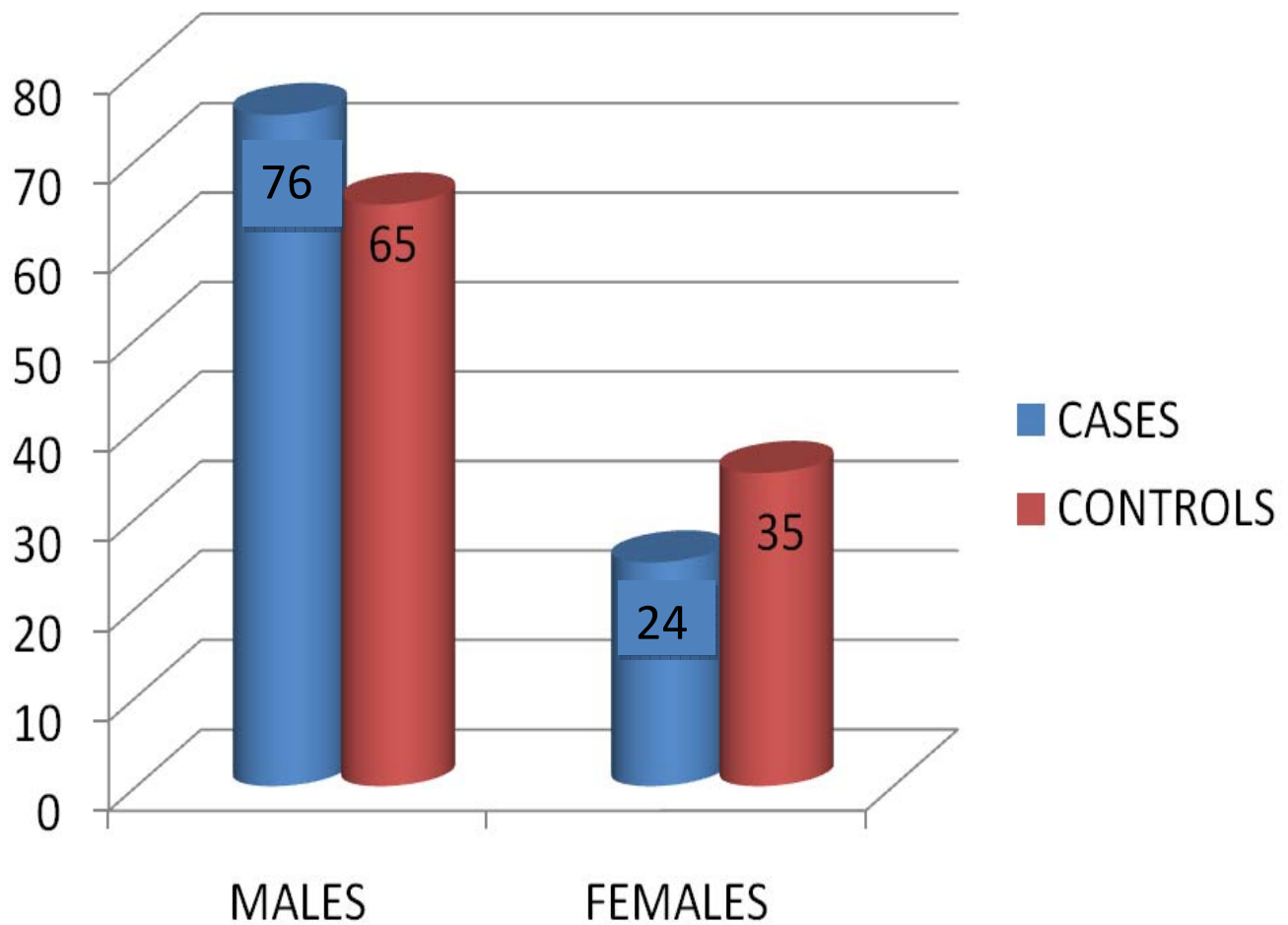


CHART 2 : SEX DISTRIBUTION

- In cases, 76% are males and 24% are females
- In controls, 65% are males and 35% are females

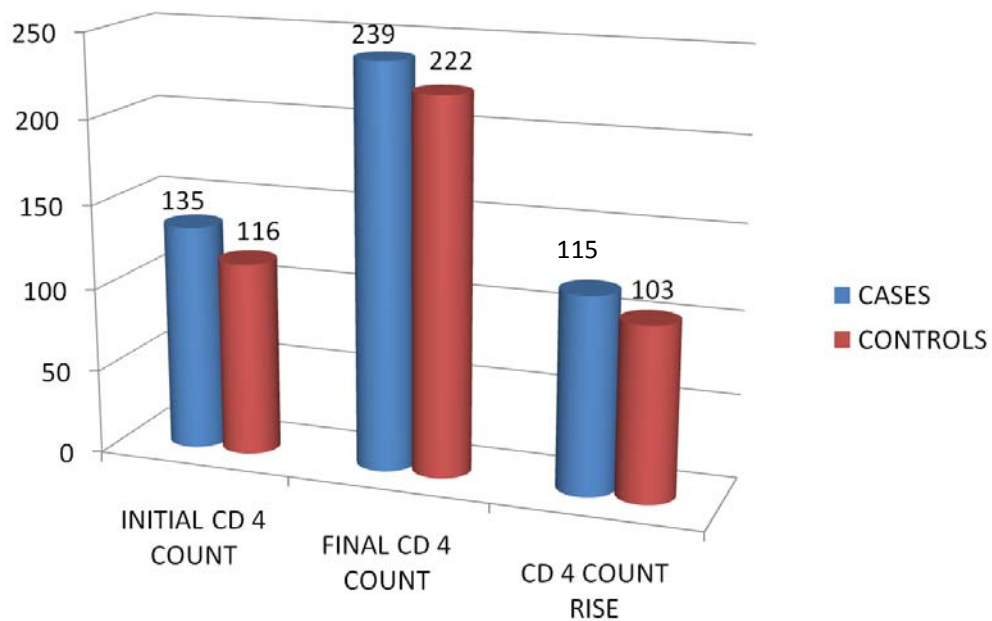


CHART 3 : CD4 DISTRIBUTION

In cases, the mean initial CD4 count is 135

the mean final CD4 count is 239

the mean CD4 count rise is 115

In controls, the mean initial CD4 count is 116

the mean final CD4 count is 222

the mean CD4 count rise is 103

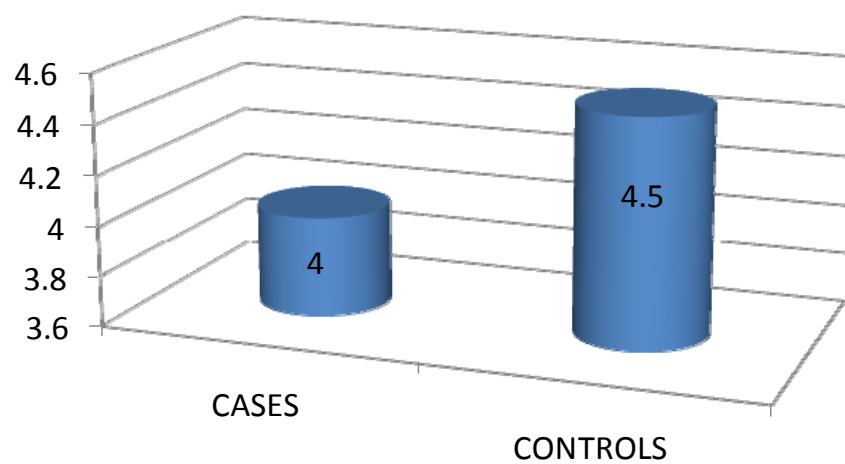


CHART 4 : MEAN DURATION OF ART

In cases the mean duration of ART was 4 months

In controls the mean duration of ART was 4.5 months

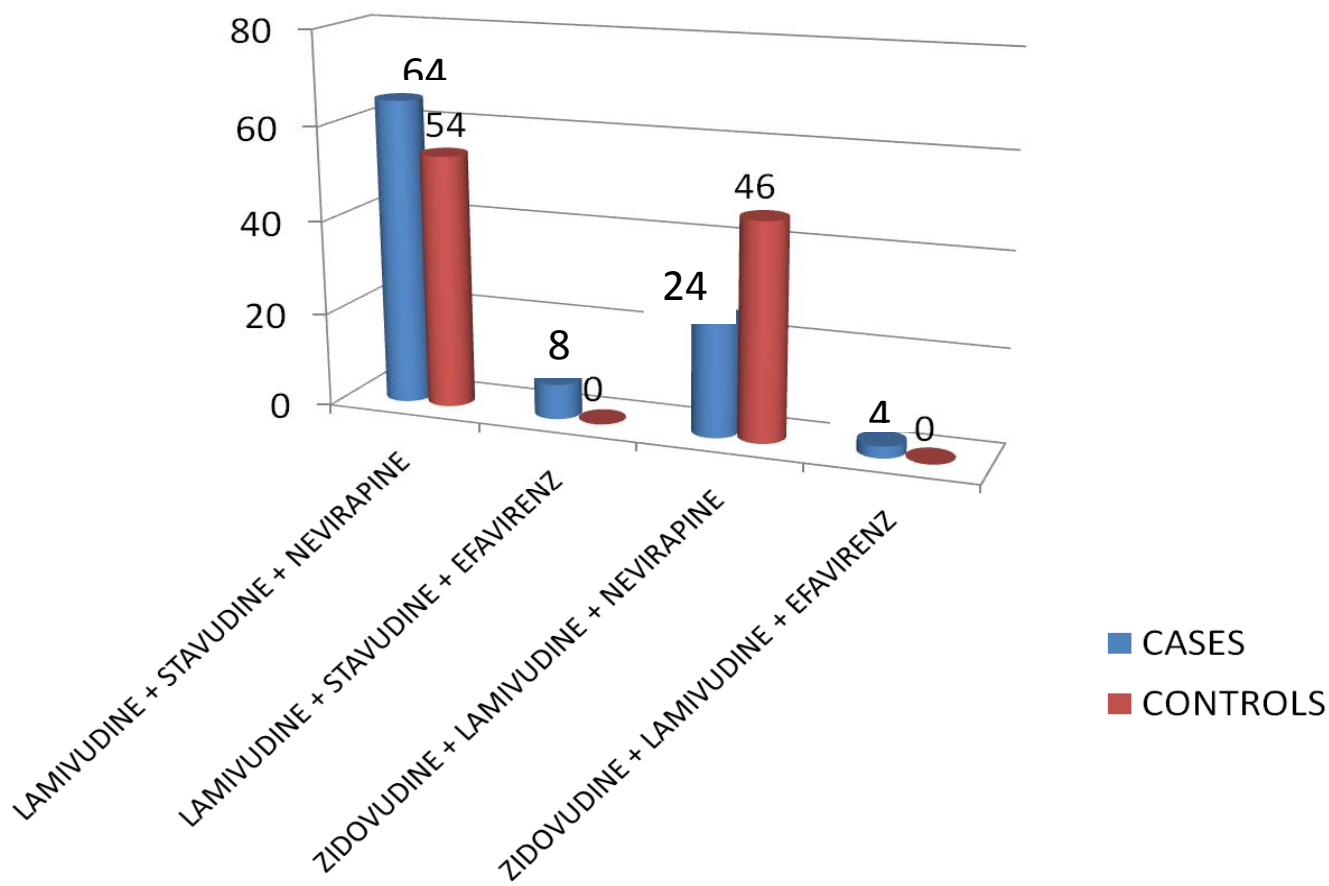


CHART 5 : TYPE OF ART

In cases -	64% were on L+S+N regimen
	24% were on Z+L+N regimen
	8% were on L+S+E regimen
	4% were on Z+L+E regimen
In controls -	54% were on L+S+N regimen
	46% were on Z+L+N regimen

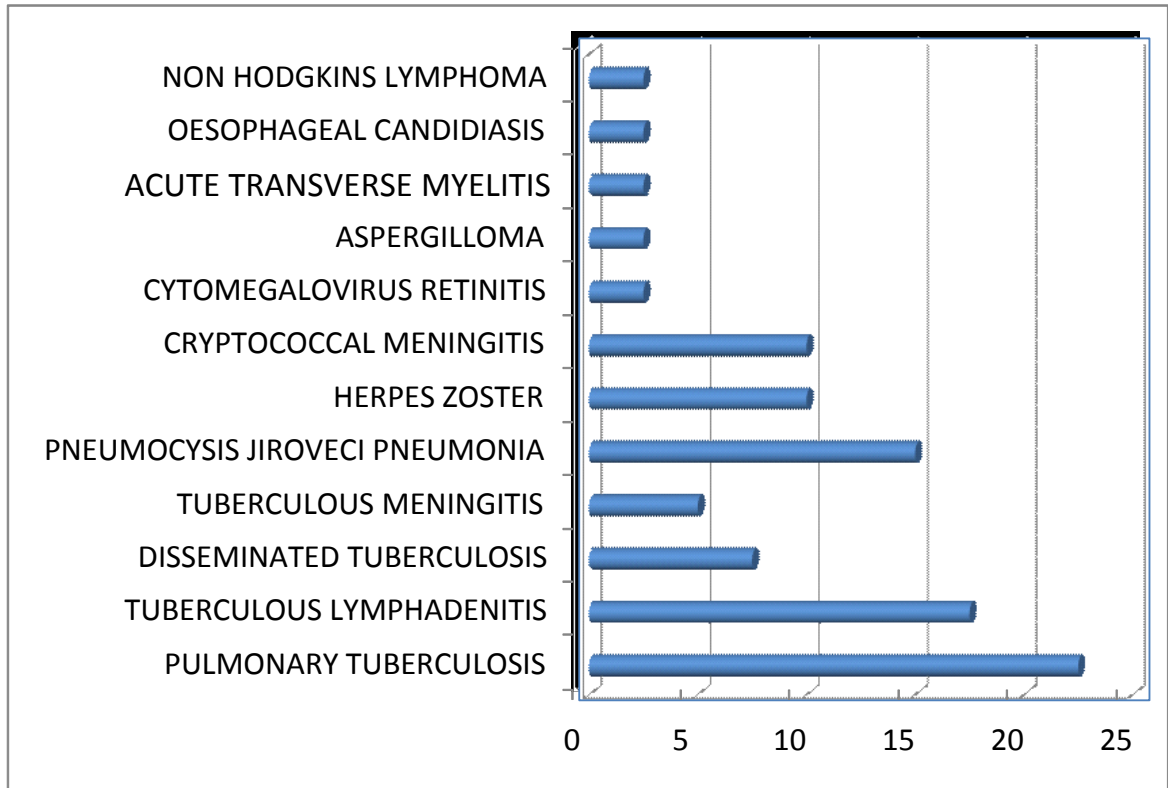


CHART 6 : TYPE OF OPPORTUNISTIC INFECTION IN THE DIAGNOSED IRIS PATIENTS

22% with Pulmonary tuberculosis

18 with Tuberculous lymphadenitis

16% with Pnuemocystis Jiroveci Pnuemonia

10% with Cryptococcal Meningitis

10% with Herpes Zoster

8% with Disseminated Tuberculosis

6% with Tuberculous Meningitis

2% with Cytomegalovirus retinitis, 2% with Oesophageal candidiasis, 2% with Aspergilloma, 2% with Non Hodgkins Lymphoma and 2% with Acute Transverse Myelitis

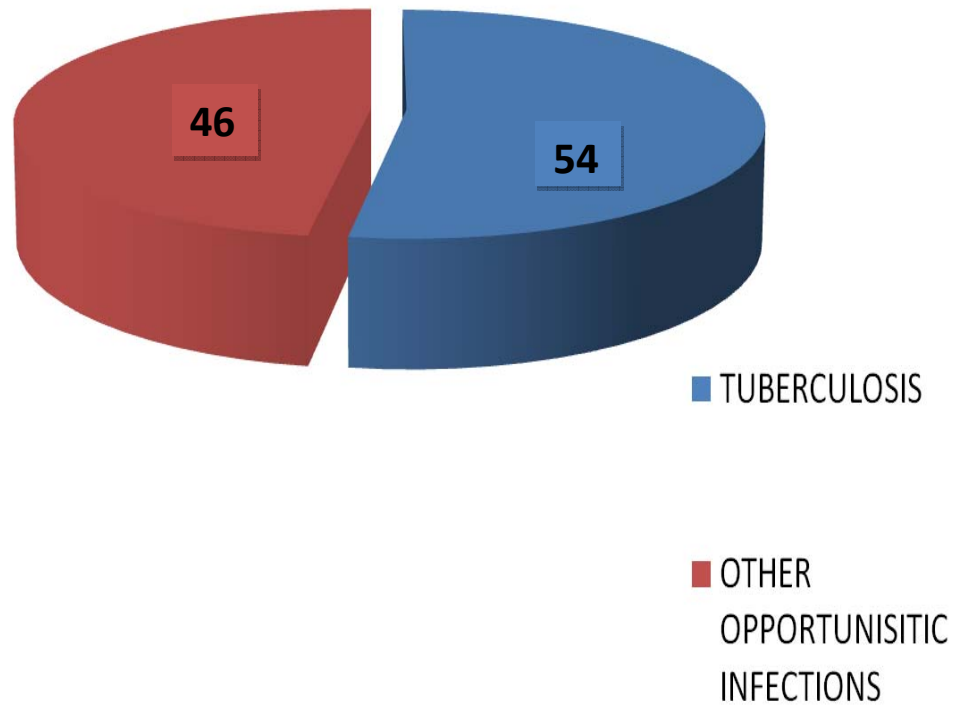


CHART 7 : TB IRIS AND OTHER OPPORTUNISTIC INFECTIONS

- 54% of the diagnosed IRIS patients had tuberculosis
- 46% constituted rest of all the opportunistic infections

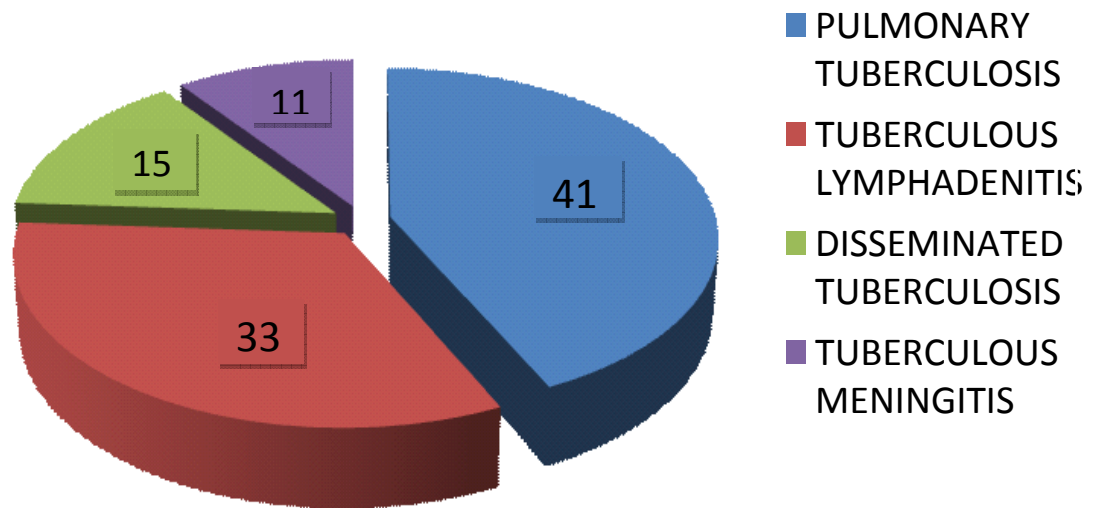
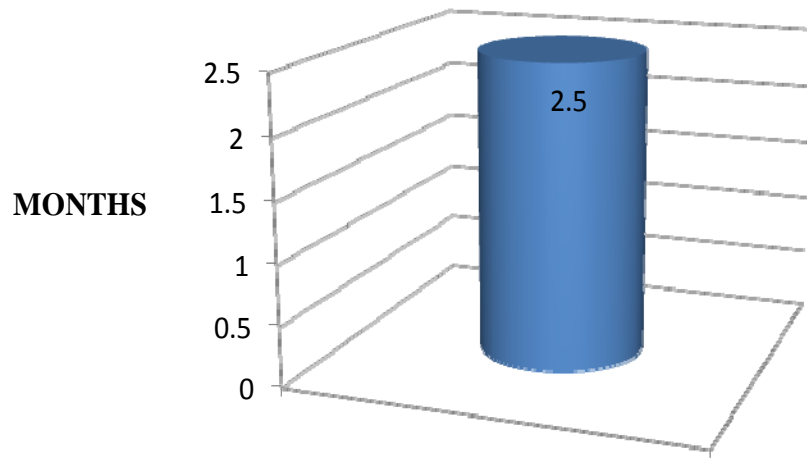


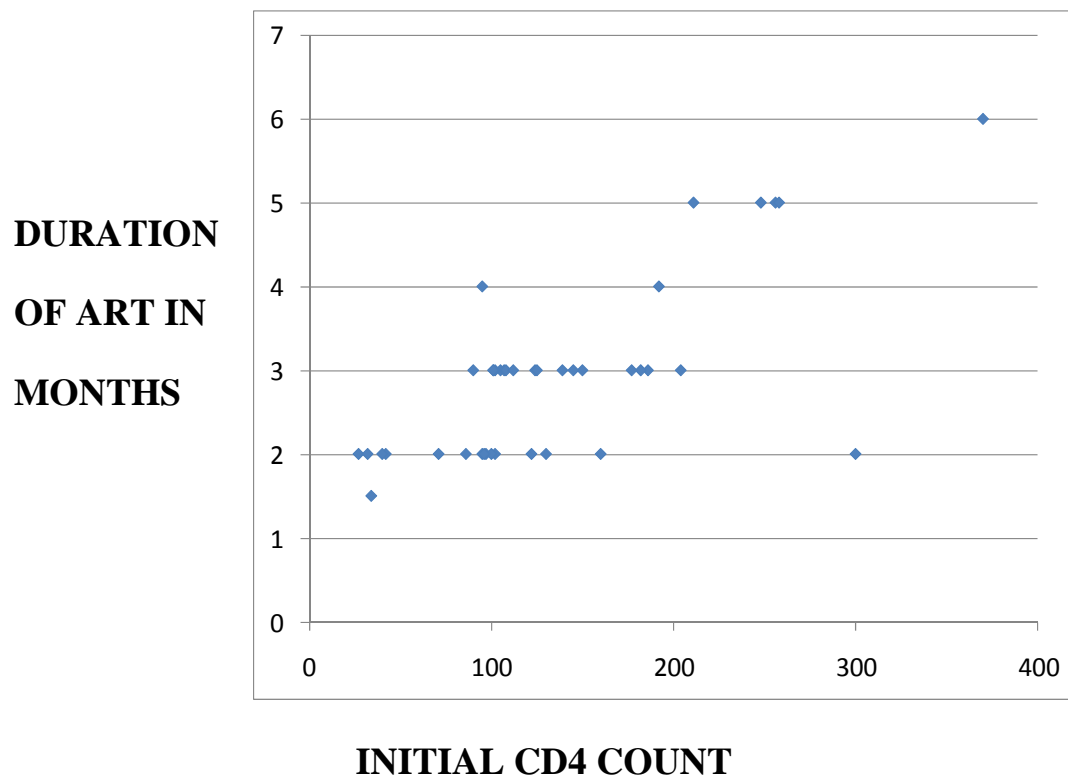
CHART 8 : SUBTYPES OF TB IRIS

- 41% with Pulmonary tuberculosis
- 33% with Tuberculous lymphadenitis
- 15% with Disseminated tuberculosis
- 11% with Tuberculous meningitis



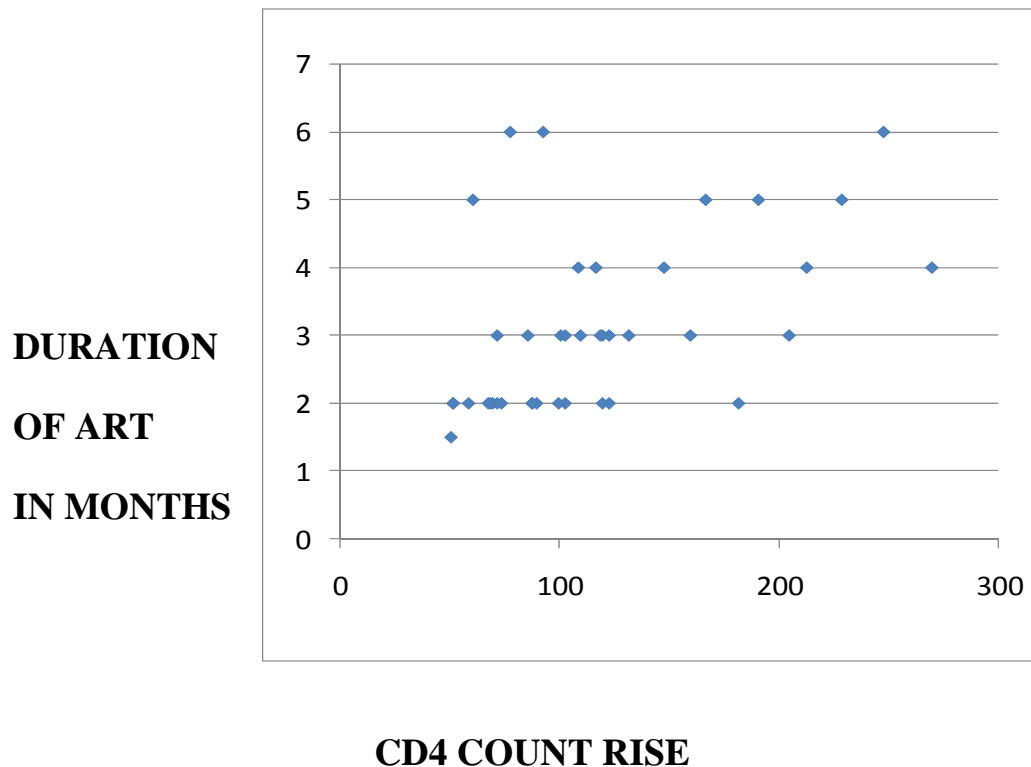
**CHART 9 : MEAN DURATION BETWEEN ATT AND ART OF
TB IRIS PATIENTS**

- The mean duration between ATT and ART of TB IRIS patients is 2.5 months



**CHART 10 : CORRELATION BETWEEN INITIAL
CD4 COUNT AND THE DEVELOPMENT OF IRIS**

- There is a weak correlation between the initial CD4 count and the development of IRIS



**CHART 11 : CORRELATION BETWEEN THE CD4 COUNT
RISE AND DEVELOPMENT OF IRIS**

- There is a weak correlation between the CD4 count rise and the development of IRIS

RESULTS :

- The mean age of the IRIS patients was **36yrs.**
- **76%** of the patients were of **male sex** and the rest **24%** were of **female sex.**
- The mean **initial CD4 count** was **135.**
- The mean **final CD4** count was **239.**
- The mean **CD4 count rise** was **115.**
- The mean **duration of ART** in IRIS patients was **4 months.**
- **64%** of the IRIS patients were on **Lamivudine + Stavudine + Nevirapine Regimen**, 24% of them on Zidovudine + Lamivudine + Nevirapine regimen, 8% were on Lamivudine + Stavudine + Efavirenz and 4% were on Zidovudine + Lamivudine + Efavirenz.
- The most common opportunistic infection was the **Pulmonary Tuberculosis**, secondly **Tuberculous Lymphadenitis** and thirdly **Pneumocystis Jiroveci Pneumonia.**
- **54%** of the IRIS patients had **Tuberculosis.**

- Among Tuberculosis patients **41%** of the patients had **Pulmonary Tuberculosis**, 33% of the patients had Tuberculous Lymphadenitis, 15% had Disseminated Tuberculosis and 11% had Tuberculous Meningitis.
- In TB IRIS patients the mean duration between ATT initiation and ART initiation was **2.5 months**.
- There is a **weak correlation** between initial CD4 count and the development of IRIS.
- There is a **weak correlation** between CD4 count rise and the development of IRIS.

DISCUSSION :

In this study a total of **50 cases** of HIV positive patients on ART who developed IRIS were identified and were matched with **80 controls** of HIV patients on ART who did not develop IRIS .

Following matching which was done for Age, Sex, CD4 count and Type of ART the opportunistic infections and their relationship to CD4 count was analysed.

- In this study the most common opportunistic infection was **Mycobacterium Tuberculosis** followed by **Pneumocystis** infection. This is in accordance with the study by Narita M (8) where Mycobacterium Tuberculosis is the most common opportunistic infection in IRIS.
- In Tuberculosis, **Pulmonary tuberculosis** was the most common opportunistic infection, secondly **Tuberculous lymphadenitis** followed by **Disseminated Tuberculosis**. This is in accordance with the study done by Lawn SD (9) where pulmonary tuberculosis was the most common type of TB IRIS.
- In our study, patients diagnosed with IRIS initiated HAART in closer proximity to the diagnosis of their opportunistic infection

compared with patients who did not develop IRIS. This is consistent with a previous report of 17 HAART-treated patients coinfecting with *M. tuberculosis* and HIV [10]

- Biological reasons for this association are unclear at present, although we speculate that patients who receive prolonged therapy for their opportunistic infection prior to starting HAART will have decreased microbial antigen burdens when HAART is initiated. This, in turn, would provide less material to stimulate a reconstituting immune system once HAART is begun. These concerns may lend added support to the recent recommendations to consider delaying HAART for 4-8 weeks after starting *M. tuberculosis* therapy in coinfecting patients [42].
- TB IRIS occurred most commonly **2.5 months** after initiating ART.

- There was weak correlation between a lower CD4 count or higher CD4 rise and the incidence of IRIS. This result was in accordance from the study by Shelburne, Samuel A(51) where a significant association between CD4 cell count rise and the diagnosis of IRIS was not seen until later in therapy .
- It has been noted that reductions in HIV-1 RNA levels in response to HAART result initially in redistribution of memory CD4 lymphocytes
- This redistribution of activated CD4 lymphocytes may be,atleast partly responsible for the manifestations of IRIS, which could explain why the rise in CD4 cell count appears delayed compared with the viral load decrease
- This result was not in accordance from the study by Lenzo N (11) where there was a strong association between a lower CD4 count the development of IRIS.

CONCLUSION:

- In our study the most common opportunistic infection in Immune Reconstitution Inflammatory Syndrome in HIV positive patients on Antiretroviral therapy is **Mycobacterium Tuberculosis** followed by **Pneumocystis** infection.
- In Tuberculosis, **Pulmonary Tuberculosis** was the most common opportunistic infection followed by **Tuberculous lymphadenitis**.
- Here, TB IRIS most commonly occurred **2.5 months** after initiating of anti retroviral therapy.
- There is a **weak correlation** between the a **lower CD4** count and the development of IRIS.
- There is a **weak correlation** between the **CD4 rise** and the development of IRIS. Hence it is vital to include HIV-1 RNA load measurement to diagnose IRIS.
- IRIS is a syndrome that occurs because a patient develops an exuberant response to appropriate therapy.

- The inclusion of IRIS in the differential diagnosis of a patient who presents with an inflammatory process after initiating HAART allows for a focused approach to diagnosis and therapy.
- These patients often require significant interventions to minimize short-term morbidity but their long-term outcome appears relatively good.
- Further studies looking at how to decrease the rate of IRIS in high-risk patients appear warranted by its prevalent nature and the association of IRIS with increased hospitalizations and invasive procedures.

LIMITATIONS :

- This is a small scale study where only 50 diagnosed cases of IRIS are analysed.
- The diagnosis of IRIS was based on only the rise in CD4 count and did not include a fall in HIV RNA levels.
- Drug Resistance to antiretroviral therapy was not ruled out.
- Drug Resistance opportunistic infection was not ruled out.

RECOMMENDATIONS :

- A large scale randomised controlled study is recommended.
- Diagnosis of IRIS should include a fall in the HIV RNA levels and a rise in CD4 count.
- Resistance testing to antiretroviral therapy should be done before a case is diagnosed as IRIS.
- Drug resistant opportunistic infection should be ruled out before diagnosing IRIS.
- Studies of early vs. deferred HAART in TB patients may provide valuable information on the optimal timing of HAART.
- Initiate HAART before CD4 drops very low.
- Exclude OI before starting HAART.

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Proforma :

1). Serial No:

2).I.P No :

3). Name:

4). Age:

5). Sex:

6). Occupation:

7). Place:

8). Duration of HIV +ve status:

9). Duration of ART:

10). Drugs :

Risk factors:	Yes	No
Male sex		
Younger age		
ART within 6 weeks		
Low baseline CD4 count at ART initiation		
Low CD4 cell percentage at ART initiation		
Lower CD4:CD8 ratio at ART initiation		
Prompt rise of CD4 count		
High bacillary burden		
Started on Protease Inhibitor (PI)		
Disseminated TB/ Extrapulm TB/Advanced TB		

CLINICAL FEATURES :

Fever :

Lymphadenopathy :

Skin lesions :

Cough :

Expectoration:

Hemoptysis :

Dyspnoea :

Chest pain:

Palpitation:

Pedal edema:

Abdominal distension:

Loose stools :

Urine output adequate /decreased

Headache :

Neck pain :

Neck Stiffness:

Vomiting :

Altered sensorium :

Seizures :

Focal Deficits :

PERSONAL HISTORY:

Smoker yes/no alcohol yes/no

DM yes/no SHT yes/no

CLINICAL FINDINGS:

Pallor:

Icterus :

Pedal edema:

Lymphnodes :

JVP

Pulse

BP

BMI

CVS

RS

INVESTIGATIONS:

Blood sugar

Urea

creatine

LFT

CHG

T.Chol

LDL

TGL

HDL

ECG

ECHO

Chest X ray :

CT chest :

Sputum AFB x 2 :

Sputum C/S :

CD 4 count (Initial)	
CD 4 count (Final)	

Others :

Clinical Spectrum :

1). Mycobacterium Tuberculosis	
2). Pneumocystis Carinii Pneumonia	
3). Cryptococcus	
4). Toxoplasmosis	
5). Cytomegalovirus	
6). Herpes Virus (Herpes Zoster and Herpes Simplex)	
7). Cryptospora and Isospora	
8). Hepatitis B virus or Hepatitis C Virus	
9). Progressive multifocal leucoencephalitis	
10). Molluscum contagiosum and genital warts	
11). Rheumatoid arthritis	
12). Systemic Lupus Erythematosus	

TREATMENT DETAILS :

OUTCOME:

ANNEXURE 2 : Masterchart Cases (50)

SR. NO	NAME	AGE	SEX	INITIAL CD4	FINAL CD4	CD 4 RISE	TYPE OF ART	DURATION OF ART (months)	OPPORTUNISTIC INFECTION	Duration if on ATT (months)
1.	Kumaran	38	M	105	193	88	L+ S+ N	6	Pulmonary Tuberculosis	3
2.	Selvi	43	F	150	201	51	Z+ L+ N	5	Pulmonary Tuberculosis	1
3.	Babu	41	M	95	118	123	L+ S+ N	6	Pulmonary Tuberculosis	2
4.	Geetha	33	F	248	307	59	L+ S+ N	5	Pulmonary Tuberculosis	4
5.	Jagadesh	34	M	160	180	120	L+ S+ N	2	Pulmonary Tuberculosis	3
6.	Sheela	29	F	256	454	248	L+ S+ N	8	Pulmonary Tuberculosis	3
7.	Ganesh	35	M	42	145	103	Z+ L+ N	2	Pulmonary Tuberculosis	
8.	Ayesha	31	F	139	330	191	Z+ L+ N	2	Pulmonary Tuberculosis	
9.	Gopal	52	M	186	255	69	L+ S+ N	4	Pulmonary Tuberculosis	2
10.	Mohan	30	M	128	207	79	L+ S+ N	3	Pulmonary Tuberculosis	2
11.	Sampath	42	M	242	374	132	Z+ L+ N	4	Pulmonary Tuberculosis	3
12.	Vasanth	48	F	204	252	78	L+ S+ N	6	Tuberculous lymphadenitis	4
13.	Ashok	35	M	107	177	70	Z + L + N	4	Tuberculous lymphadenitis	
14.	Asraf	28	M	124	225	101	L + S + E	6	Tuberculous lymphadenitis	2
15.	Selva	37	M	211	272	61	L+ S+ N	5	Tuberculous lymphadenitis	

16.	Ravi	44	M	102	250	148	L+ S+ E	2	Tuberculous lymphadenitis	1
17.	Renuka	25	F	182	275	93	Z+ L+ N	6	Tuberculous lymphadenitis	
18.	Ganamurthy	42	M	122	304	182	L+ S+ N	2	Tuberculous lymphadenitis	
19.	Manohar	27	M	60	188	128	L+ S+ N	2	Tuberculous lymphadenitis	
20.	Naveenbabu	45	M	102	202	100	L+ S+ N	6	Tuberculous lymphadenitis	1
21.	Gajendiran	33	M	27	136	109	Z+ L+ N	4	Disseminated Tuberculous	3
22.	Yasim	28	M	101	220	119	L+ S+ N	3	Disseminated Tuberculosis	2
23.	Seetha	42	F	370	537	167	L+ S+ E	5	Disseminated Tuberculosis	2
24.	Ganesan	40	M	210	315	105	L+ S+ N	5	Disseminated Tuberculosis	4
25.	Partheeban	41	M	97	214	117	Z+ L+ E	4	Tuberculous Meningitis	
26.	Vinoth	32	M	82	193	111	Z+ L+ N	7	Tuberculous Meningitis	3
27.	Pravin	34	M	40	150	90	L+ S+ N	2	Tuberculous Meningitis	
28.	Jagadesh	34	M	192	264	72	L+ S+ N	6	PCP Pneumonia	
29.	Ashiya	28	F	32	261	229	L+ S+ N	2	PCP Pneumonia	
30.	RamaKrishna	30	M	86	154	68	L+ S+ N	6	PCP Pneumonia	
31.	Narayanan	39	M	300	370	270	Z+ L+ N	2	PCP Pneumonia	
32.	Padmavathy	32	F	90	176	86	Z+ L+ N	3	PCP Pneumonia	
33.	janardhanan	39	M	100	172	72	L+ S+ N	2	PCP Pneumonia	
34.	Aranya	34	F	160	294	134	L+ S+ E	5	PCP Pneumonia	
35.	Raman	38	M	145	250	105	L+ S+ N	4	PCP Pneumonia	
36.	Abdul Khader	39	M	71	276	205	Z+ L+ N	3	Cryptococcal Meningitis	
37.	Harish	45	M	102	205	103	L+ S+ N	3	Cryptococcal Meningitis	
38.	Asif	31	M	34	144	110	L+ S+ N	2	Cryptococcal Meningitis	
39.	Surendaran	38	M	95	308	213	L+ S+ N	4	Cryptococcal Meningitis	
40.	Jebastian	47	M	150	216	66	L+ S+ N	5	Cryptococcal Meningitis	

41.	Ashok	37	M	177	265	88	L+ S+ N	2	Non Hogkins Lymphoma	
42.	Prema	33	f	125	199	74	L+ S+ N	2	Herpes Zoster	
43.	Suresh Kumar	36	M	101	153	52	L+ S+ N	5	Herpes Zoster	
44.	Salim	27	M	108	240	132	L+ S+ N	4	Herpes Zoster	
45.	Abdul	31	M	145	268	123	Z+ I+ N	3	Herpes Zoster	
46.	Sarumathi	25	F	49	133	84	Z+ L+ E	8	Herpes Zoster	
47.	Ismail	45	M	112	132	120	L+ S+ N	6	CMV Retinitis	
48.	Satish	49	M	96	256	160	L+ S+ N	7	Aspergilloma	
49.	Sethu	34	M	258	310	52	L+ S+ N	1.5	Acute Transverse myelitis	
50.	Peter	34	M	130	230	100	L+ S+ N	2	Oesophageal Candidiasis	

ANNEXURE 3 – Masterchart Controls (80)

SR.NO	NAME	AGE	SEX	INITIAL CD 4	FINAL CD 4	CD 4 RISE	REGIMEN	DURATION OF ART (months)
1.	abdulla	50	M	164	268	104	3	6
2.	venkatesh	40	M	189	298	193	3	9
3.	mallika	30	F	139	332	119	3	9
4.	devaki	30	F	103	279	76	3	3
5.	sukanya	35	F	67	189	122	1	3
6.	wilfred	35	M	87	171	84	3	3
7.	janardhan	32	M	107	209	102	3	3
8.	chandra	47	F	139	225	86	3	9
9.	susheela	47	F	160	225	65	3	3
10.	Kumari	46	F	50	170	120	3	3
11.	rajkumar	53	M	144	212	68	3	3
12.	Mani	54	M	181	279	98	3	5
13.	Ashok	53	M	152	283	131	3	6
14.	manohar	38	M	128	225	61	3	9
15.	Harish	40	M	11	138	127	3	6
16.	Anandan	38	M	153	369	216	3	6
17.	Jagadish	33	M	90	160	70	3	6
18.	Santhosh	37	M	139	220	81	3	6
19.	George	53	M	142	212	68	3	9
20.	Vasanthi	38	F	75	280	205	3	6
21.	Janardan	36	M	126	235	99	3	3
22.	Susheela	32	F	124	176	52	3	5
23.	Jayaram	43	M	169	385	216	3	3
24.	Bhaskar	38	M	180	329	149	3	6
25.	Prema kumari	36	F	70	181	111	3	3

26.	Chandravathi	30	F	165	323	158	3	6
27.	Anandkumar	42	M	57	108	51	3	3
28.	Jagannath	38	M	18	83	65	3	6
29.	Balraj	34	M	175	262	87	3	6
30.	Lakshmi	34	F	186	291	105	3	3
31.	Sarojini	35	F	167	259	92	3	3
32.	Venkatraman	47	M	64	180	116	3	3
33.	Ganga	65	F	76	158	82	1	3
34.	Shobana	36	F	169	228	59	1	9
35.	Venkatesan	38	M	70	198	128	1	3
36.	Salima	35	F	175	256	81	1	9
37.	Narayanan	46	M	175	258	83	3	3
38.	Ashok	30	M	71	138	67	3	3
39.	Bashir	39	M	65	280	215	1	3
40.	Mohammed	55	M	180	250	70	1	3
41.	Palani	49	m	176	292	116	1	3
42.	Ameer	46	m	193	249	56	3	6
43.	Divya	58	f	114	178	64	3	3
44.	Sita	66	f	168	238	70	3	3
45.	Vimala	32	F	133	245	112	1	2
46.	Karthick	44	M	89	254	165	1	2
47.	Pari	38	M	120	222	102	1	3
48.	Narayanan	39	M	79	189	110	1	3
49.	Vinoth	27	M	144	235	91	1	4
50.	Kavitha	45	F	65	189	124	1	1
51.	Vincent	46	M	122	189	67	1	3
52.	Abdulla	36	M	113	189	73	1	8
53.	Sukumar	37	M	90	176	86	1	3
54.	Hemanth	50	M	88	183	95	1	3
55.	Ayesha	33	F	112	234	122	1	4

56.	Abdul Rahman	41	M	47	157	110	1	2
57.	Rakesh	36	M	160	220	60	1	5
58.	Partheeban	43	M	100	198	98	1	3
59.	Moorthy	39	M	59	178	119	1	7
60.	Jagadesh	39	M	97	178	81	1	4
61.	Ashiya	33	F	89	190	101	1	6
62.	RamaKrishnan	29	M	80	279	199	1	3
63.	Narayanan	34	M	130	278	148	1	2
64.	Padmavathy	43	F	120	220	100	1	4
65.	Janardhanan	42	M	118	201	83	1	3
66.	Abdul Khader	40	M	47	150	103	1	5
67.	Harish	33	M	89	210	121	1	6
68.	Asif ali	38	M	79	130	51	1	3
69.	Surendaran	35	M	101	220	119	1	4
70.	Parvathy	40	F	90	173	83	1	5
71.	Dinesh	33	M	87	186	99	3	7
72.	George	38	M	69	130	61	1	2
73.	Harikumar	46	M	220	301	81	1	5
74.	Lavanya	27	F	145	237	92	1	6
75.	Manohar	37	M	92	176	84	1	3
76.	Padmini	39	F	90	145	55	1	4
77.	Ramanathan	33	M	110	230	120	1	4
78.	Sathyanarayana	42	M	167	234	67	1	6
79.	Rohini	39	F	88	277	129	1	4
80.	Pushpa	32	F	134	236	102	3	5

Regimens : 1- Lamivudine + Stavudine + Nevirapine

2 – Zidovudine + Lamivudine + Nevirapine

3 – Lamivudine + Stavudine + Efavirenz

4 – Zidovudine + Lamivudine + Efavirenz

ABBREVIATIONS

IRIS :	Immune Reconstitution Inflammatory Syndrome
ART :	Anti Retroviral therapy
CRP :	C-Reactive Protein
CMV :	Cytomegalovirus
HSV :	Herpes Simplex Virus
MAC :	Mycobacterium avium complex
LDH :	Lactate dehydrogenase
PCP:	Pneumocystis Carinii Pneumonia
PCR :	Polymerase Chain Reaction

PATIENT CONSENT FORM

Study detail.

Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV +ve patients on Anti Retroviral therapy (ART)

Study centre :Institute of internal medicine / Madras Medical College- ART centre
Patients Name :

Patients Age :

Identification number :

Patient may check (✓) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.

☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of current study and any further research that may be conducted in relation to it, even I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

☐

I hereby consent to participate in this study.

☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological .biochemical, radiological tests.

☐

Signature/thumb impression: place date

Patients Name and Address:

Signature of investigator : place date

Study investigator's Name :